



111-#1030.00
DAIC for Patents

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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IN RE : U.S. PATENT 4,250,334
ISSUED : FEBRUARY 10, 1981
TO : CLIFFORD L. COON & ROBERT L. SIMON
FOR : METHOD OF SYNTHESIZING
FLUOROMETHYLHEXAFLUOROISOPROPYL ETHER

Assistant Commissioner of Patents
Washington, D.C. 20231

**APPLICATION FOR EXTENSION OF PATENT
TERM UNDER 35 U.S.C. §156**

Sir:

Your Applicant, Baxter International, Inc. (formerly, Baxter Travenol Laboratories, Inc.), a corporation existing under the laws of Delaware, represents that it is the assignee of the entire interest in and to Letters Patent of the United States of America No. 4,250,334, granted to Clifford L. Coon and Robert L. Simon on the 10th day of February 1981, for a **METHOD OF SYNTHESIZING FLUOROMETHYLHEXAFLUOROISOPROPYL ETHER** by virtue of an assignment in favor of Baxter Travenol Laboratories, Inc., recorded March 17, 1980, Reel 3740, Frame 640. Your Applicant, acting through the undersigned attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office under 37 C.F.R. §1.740. For the convenience of the Patent and Trademark Office, the information submitted in this application will be presented in a format which will follow the requirements of 37 C.F.R. §1.740.

(1) Sevoflurane (marketed by Abbott Laboratories under the tradename, Ultanetm), which contains as the active ingredient, fluoromethyl-1,1,1,3,3,3-hexafluoroisopropyl ether

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[also known as fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether].

(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. §355).

(3) The approved product, Sevoflurane, received permission for commercial marketing or use as an anesthetic under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) on June 7, 1995.

(4) The only active ingredient in Sevoflurane is fluoromethyl-1,1,1,3,3,3-hexafluoroisopropyl ether, which had not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 20-478 by the Food and Drug Administration on June 7, 1995.

(5) This Application for extension of patent term under 35 U.S.C. §156 is being submitted within the the 60 day period pursuant to 37 C.F.R. §1.720(f), said period which will expire on August 7, 1995.

(6) The complete identification of the patent for which extension is being sought is as follows:

Inventor(s): Clifford L. Coon and Robert L. Simon

Patent Number: 4,250,334

Issue Date: February 10, 1981

Expiration Date: December 26, 1999, as determined by 35 U.S.C. §154(c) enacted pursuant to the General Agreement of Tariffs and Trade (GATT), [Pub. L. No 103-465 (H.R.5110), signed December 8, 1994, effective January 1, 1995].

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Note that the original expiration date of the patent, prior to 35 U.S.C. §154(c) implementation, would be February 10, 1998.

(7) See "Exhibit A" for a complete copy of the patent identified in paragraph (6) hereof.

(8) No Terminal Disclaimer, Certificate of Correction or Re-examination Certificate has been issued with regard to U.S. Patent 4,250,334. No maintenance fee payment is required for U.S. Patent 4,250,334 (37 C.F.R. §1.362(a)).

(9) U.S. Patent 4,250,334 claims a method for synthesizing the active ingredient in Sevoflurane, fluoromethyl-1,1,1,3,3,3-hexafluoroisopropyl ether. Specifically the method for synthesizing fluoromethyl-1,1,1,3,3,3-hexafluoroisopropyl ether is claimed in claims 1-4.

Claim 1 reads as follows:

1. The method of synthesizing fluoromethyl-1,1,1,3,3,3-hexafluoroisopropyl ether which comprises adding hexafluoroisopropyl alcohol to a mixture comprising a stoichiometric excess of formaldehyde and hydrogen fluoride, plus sufficient sulfuric acid to sequester most of the water produced by the reaction, said mixture being maintained at a temperature of at least 57°C to cause vapor formation by boiling of the fluoromethylhexafluoroisopropyl ether formed; and collecting and condensing said vapor.

The method for synthesizing the approved product, Sevoflurane, is synthesized in a single pass step by the reaction of paraformaldehyde (formaldehyde), hydrogen fluoride (HF), fuming sulfuric acid (oleum) and hexafluoroisopropanol (HFIP) at a temperature of about 65°C (the temperature of the reaction mixture is moderately elevated from room temperature to approximately 65°C under agitation). The gassified, crude Sevoflurane

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mixture produced by the reaction mixture heating is passed through a condenser to condense the gaseous Sevoflurane and collected in a vessel containing water. The hydrogen fluoride is the solvent for the reactant as well as the fluorinating agent and is included in an excess. Oleum serves as the dehydration agent (sequesters water) to catalyze the reaction of paraformaldehyde with HFIP to form fluoromethyl-1,1,1,3,3,3-hexafluoroisopropyl ether (Sevoflurane). An excess mole ratio of paraformaldehyde is used in the reaction.

Claim 2 reads as follows:

2. The method of claim 1 including the step of thereafter purifying fluoromethylhexafluoroisopropyl ether from said condensed vapor.

After the reaction step as described above, the condensed and collected Sevoflurane is subjected to further purification, including a hydrogen fluoride absorption step in water (to remove hydrogen fluoride from the crude condensed Sevoflurane); a sulfuric acid wash to remove bis-fluoromethyl ether, a low boiling impurity which is formed during the reaction step; a first caustic soda wash step to remove unreacted HFIP; a distillation step to further purify the crude Sevoflurane from the first caustic soda wash step; a second caustic soda wash to remove any remaining HFIP; a water wash to remove any sodium hydroxide left after the second caustic soda wash step and a dehydration step to remove water.

Claim 3 reads as follows:

3. The method of claim 1 in which said formaldehyde is paraformaldehyde.

Paraformaldehyde is used as the source of formaldehyde in the method of synthesizing Sevoflurane.

Claim 4 reads as follows:

The method claim of 1 in which said mixture is maintained at a temperature of 60°C to 70°C.

During the synthesis of Sevoflurane, the temperature of the reaction mixture is moderately elevated from room temperature to approximately 65°C under agitation and is maintained at the temperature of 65°C for a considerable period to ensure vaporization of Sevoflurane in order to condense and collect the product in a water-containing vessel.

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(10) The relevant dates and information pursuant to 35 U.S.C §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) Investigational New Drug Application (IND 27,645) for Sevoflurane was filed on December 20, 1985 and became effective on January 10, 1985.

(ii) New Drug Application (NDA 20-478) for Sevoflurane was submitted on July 8, 1994; and

(iii) New Drug Application (NDA 20-478) was approved on June 7, 1995.

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(11) As a brief description of the activities undertaken by Applicant, Applicant's licensees, Maruishi Pharmaceutical Co., Ltd. (by its agent Besselaar) and Abbott Laboratories, during the applicable regulatory period, attached hereto as "Exhibit B" is a chronology of the activities undertaken by or communications made between Applicant or Applicant's licensees or agents and the FDA from December 20, 1985 until June 7, 1995.

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(12) Applicant is of the opinion that U.S. Patent No. 4,250,334 is eligible for extension under 35 U.S.C. §156 because it satisfies all of the requirements for such extensions as follows:

(a) 35 U.S.C. §156(a)

U.S. Patent 4,250,334 claims a method of manufacturing a product.

(b) 35 U.S.C. §156(a)(1)

The term of U.S. Patent 4,250,334 has not expired before submission of this application.

(c) 35 U.S.C. §156(a)(2)

The term of U.S. Patent 4,250,334 has never been extended.

(d) 35 U.S.C. §156(a)(3)

The application for extension is submitted by the owner of record in accordance with 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. §156(a)(4)

The product, Sevoflurane, has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. §156(a)(5)(A)

The commercial marketing or use of the product, Sevoflurane, after the regulatory review period is

the first permitted commercial marketing or use of the product under the provision of the Federal, Food, Drug and Cosmetic Act (21 U.S.C. §355) under which such regulatory review period occurred.

(g) 35 U.S.C. §156(c)(4)

No other patent has been extended for the same regulatory review period for the product, Sevoflurane.

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(13) The length of extension of the patent term of U.S. Patent 4,250,334 claimed by Applicant is 5 years or 1,826 days. The length of the extension was determined pursuant to 37 C.F.R. §1.775 as follows:

(a) The regulatory period under 35 U.S.C. §156(g)(1)(B) began on January 10, 1986 and ended on June 7, 1995, which is a total of 3,435 days or 9.41 years, which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. §156(g)(2)(B)(i), the "Testing Period", began on January 10, 1986 and ended on July 7, 1994, which is 3,101 days or 8.49 years and

(ii) The period of review under 35 U.S.C. §156(g)(2)(B)(ii), the "Application period", began on July 8, 1994 and ended on June 7, 1995, which is 334 days or 0.92 years.

(b) The regulatory review period upon which the period of extension is calculated is the entire review period as determined in sub-paragraph (13)(a) above (3,435 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (February 10, 1981) which is 0 days, and

(ii) The number of days during which applicant's licensees did not act with due diligence which is zero (0) days, and

(iii) One-half the number of days determined in sub-paragraph (13)(a)(i) after the patent issued $[(3101-0)/2]$ or 1,551 days which totals 1,884;

(c) The number of days as determined in sub-paragraph (13)(b) (1,884 days) when added to the original term of the patent (December 26, 1999, as determined by 35 U.S.C. §154(c))

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would result in the date, February 21, 2005;

(d) Fourteen (14) years when added to the date of the NDA approval (June 7, 1995) would result in the date June 7, 2009;

(e) The earlier date as determined in sub-paragraphs (13)(c) and (13)(d) is February 21, 2005;

(f) Since the original patent was issued before September 14, 1984 and a request for an exemption was not submitted before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, five (5) years when added to the original expiration date of the patent (December 26, 1999) would result in the date December 26, 2004.

(g) The earlier date as determined in sub-paragraph (13)(e) and (13)(f) is December 26, 2004.

(14) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought. To that end, Applicant provides the information set forth in attached Exhibits C and D.

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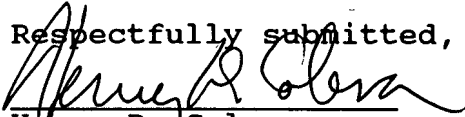
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(15) The prescribed fee of \$1,030.00 for receiving and acting upon this application is enclosed. The Commissioner is authorized to charge any deficiency in the enclosed fee or credit any overpayment to deposit account 04-0838. The requisite declaration pursuant to 37 C.F.R. §1.740(b) is attached hereto as Exhibit E.

Dated: August 7, 1995

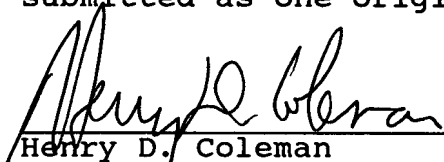
Exhibits

Respectfully submitted,


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Regis. No. 32,559
Attorney for Applicant(s)
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New York, New York 10016
(212) 338-9080

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. §156, including its Exhibits and supporting papers is being submitted as one original and five (5) copies thereof.


Henry D. Coleman

Dated: August 7, 1995

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EXHIBIT B

SEVOFLURANE
Chronology of Events

IND	NDA	DATE	EVENT
27645	20-478		
X		12/20/85	IND Submitted by Anaquest (Baxter Travenol Licensee)
X		1/10/86	IND 27645 Assigned
X		2/10/86	Receipt of Deficiency Letter Dated 2/06/86
X		3/04/86	Letter to D. Smith requesting re-evaluation
X		10/17/86	Submitted 1986 Annual Report, No Activity
X		07/10/87	Transfer IND 27,645 from Anaquest to Baxter Travenol
			Submitted summary of the results of MAC study conducted under the sponsorship of Anaquest
			Submitted clinical summary in Japan conducted under the sponsorship of Maruishi
X		06/29/89	Transfer IND from Baxter Travenol to G.H. Besselaar Associates as agent for Maruishi Pharmaceutical Co., Ltd., Osaka, Japan (Baxter Travenol Licensee)
			Submitted chemistry, manufactur- ing and control information by Central Glass Co., Ltd., contract manufacturer and by Maruishi.
			Submitted pharmacology, toxicol- ogy and previous experiments in human patients conducted by Maruishi.
X		08/07/89	Submitted updated investigators' brochure and protocol for Phase II open-label study.

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EXHIBIT B Page 2
Sevoflurane Chronology of Events

IND	NDA	DATE	EVENT
27645	20-478		Requested meeting with FDA prior to initiation of Phase II study
X		10/23/89	Submitted copy of the kinetics and metabolism study (Phase I) conducted by Dr. Eger
X		10/25/89	FDA (Dr. Landesman) requested to amend protocol for Phase II
X		01/08/90	Submitted revised protocol for Phase II study and additional information concerning the chemistry, manufacturing and control
X		02/23/90	Requested meeting with FDA
X		03/27/90	Confirmed request for meeting with medical reviewers and others in FDA
X		03/28/90	Submitted amendment for change of Phase II protocol
X		07/10/90	Response to the FDA- request for information
			Request meeting with FDA in September, 1990 before Phase III study
X		09/05/90	Submitted annual progress report since the transfer of the sponsorship of IND from Baxter to Besselaar (agent of Maruishi in FDA) for Phase II study
X		10/05/90	Request re-scheduled meeting with FDA which was postponed
X		02/26/91	Submitted annual progress report
X		03/28/91	Responded to FDA request for additional information

EXHIBIT B Page 3
Sevoflurane Chronology of Events

IND 27645	NDA 20-478	DATE	EVENT
X		04/19/91	Meeting with FDA Anesthetic Advisory Committee. FDA recommended three studies: 1) rat focal ischemia; 2) response to vasopressin; and 3) cardiovascular effect in man.
X		03/02/92	Submitted annual progress report
X		10/06/92	Transferred IND from Besselaar to Abbott Laboratories
X		10/06/92	FDA acknowledged Abbott as Sponsor for IND
X		01/07/93	Special Submission
X		01/26/93	Annual Report submitted
X		05/13/93	General Correspondence- Chemistry Review
X		05/17/93	Submitted proposed advisory panel book
X		12/08/93	Information Amendment- Pharmacology-Toxicology
X		01/25/94	Annual Report submitted
X		02/21/94	General Correspondence- Informational packet for 3/8/94 Pre-NDA Meeting
X		03/08/94	Pre-NDA Meeting
X		04/12/94	General Correspondence- Amend Clinical Summary Report
X		04/29/94	NDA Presubmission
X		05/09/94	FDA Teleconference
X		05/20/94	Information Amendment Pharmacology-Toxicology

EXHIBIT B Page 4
Sevoflurane Chronology of Events

IND 27645	NDA 20-478	DATE	EVENT
X		05/27/94	General Correspondence- Final Version of 5/9/94 FDA/Abbott Teleconference Minutes
	X	07/08/94	Original NDA submitted
	X	07/19/94	Information Amendment Pharmacokinetics
	X	07/27/94	Study Summaries and Insert Provided
	X	10/28/94	Clinical Summary Report
	X	11/28/94	Copies of Method Validation (FDA Request)
	X	12/07/94	Amendment to provide Clinical Summary Report
	X	12/12/94	Amend to include LDA from Central Glass Co.
	X	12/21/94	Request Name Change (Ultane) for Review/Acceptability Revision to Package Insert
	X	02/14/95	Annual Report
	X	03/17/95	Amend per 3/15/95 Labelling Comments for FDA (Change Name to Ultane)
	X	03/21/95	Provided Phase IV Post-Marketing Commitments Provided Reference Standards to St. Louis District Office Provided Debarrment Statement
	X	04/03/95	FDA Request for Ultane Promotional Material
	X	04/06/95	Response to FDA letter of 4/4/95 Regarding labelling. Draft Labels Provided.

EXHIBIT B Page 5
Sevoflurane Chronology of Events

IND	NDA	DATE	EVENT
27645	20-478		
	X	06/07/95	Approval of Original NDA. Submit FPL and Promotional Pieces.

EXHIBIT C

Sevoflurane was first synthesized at Travenol Laboratories during the late 1960s as part of a comprehensive effort to find inhalational anesthetic agents that might have safety and efficacy advantages over Halothane. Sevoflurane was first reported by Regan, Wallin and their colleagues and results of animal studies were published by Wallin, et al., Anesth. Analg., 54, 758, (1975).

Travenol Laboratories began to study the agent in the United States and filed for regulatory approval in 1976. In July, 1976, Travenol Laboratories filed an original submission with the United States FDA which was assigned IND 12,639. Further information regarding steps taken by Travenol Laboratories in furtherance of the regulatory process under IND 12,639 are attached hereto as Exhibit D. IND 12,639 never matured into a new drug application (NDA) for Sevoflurane.

Travenol Laboratories conducted preliminary studies at Northwestern University and the University of Miami between 1976 and 1978. After initial studies, Travenol Laboratories contracted with Maruishi Pharmaceutical Company ("Maruishi") in 1983 for final development of the agent in Japan and with Anaquest (a division of BOC, Inc.) in 1985 for further development in the United States.

After preliminary studies in dogs (T. Kazama and K. Ikeda, [Abstract] Anesthesiology, 60, A17, 1985), Maruishi proceeded with clinical studies in humans (over 1600 patients in 1985-1987). In 1985, Anaquest re-initiated studies on Sevoflurane in the United States under IND 27,645. In July, 1987, Anaquest discontinued development of the drug for business reasons and returned the drug to Travenol Laboratories.

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Maruishi separately proceeded with regulatory approval in Japan and obtained marketing approval in January, 1990. Maruishi then decided to develop Sevoflurane in the United States and worked with a clinical research organization (G.H. Besselaar and Associates) to develop a clinical plan for obtaining regulatory approval in the United States. In 1992, Abbott Laboratories executed a license agreement and Abbott Laboratories assumed responsibility for obtaining regulatory approval to cover global registration. Abbott initiated activities in the United States FDA in October, 1992, filed NDA 20-478 in July 1994 and obtained approval on June 7, 1995.

EXHIBIT D

SEVOFLURANE
Chronology of Events of IND 12,639

DATE	EVENT
07/19/76	Original Submission.
07/23/76	Acknowledgement; Number 12,639 Assigned
08/03/76	Request that IND be considered on clinical hold
08/13/76	Recommendation that initial studies be conducted in human volunteers
10/05/76	Response submitted to recommendation. Dr. Bruce replaces Dr. Eckenhoff as primary investigator
11/11/76	Deficiency Letter sent from FDA
12/16/76	Addition of Donald J. Funk as co-investigator with Dr. Bruce
03/14/77	Submitted clinical reports; notification to terminate work at Northwestern University
03/30/77	Submission of inorganic fluoride values
04/07/77	Addition of Duncan A. Holiday, M.D. as investigator
08/11/77	Submitted Annual Progress Report
05/31/78	Submitted response re deficiency letter; with attachments and enclosures
07/26/78	Submitted correction of error in 5/31/78 submission; submitted amendment
07/27/78	Submitted annual progress report with enclosure
09/11/78	Request for additional information re pharmacology
10/10/78	Submitted response re above
11/07/78	Submitted response to 9/11/78 letter; attachments

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DATE	EVENT
01/09/79	Submitted request for meeting to discuss protocol for Phase II study
02/20/79	Submitted response to telephone request for submission of a protocol for Phase II clinical studies
03/02/79	Deficiency letter
06/16/79	Submitted results of Phase I study and proposed protocol for Phase 2 testing; attachments
07/24/79	Submitted annual progress report; 06/19/79 submission attached
07/24/80	Submitted annual progress report
07/27/81	Submitted annual progress report
07/20/82	Submitted annual progress report
09/28/83	Submitted letter to keep exemption active for future clinical studies
07/30/84	Submitted change in sponsor responsibility, official correspondent and notice of Maruishi development in Japan and authorization of Maruishi/Bio/dynamics interaction with the FDA on this file
07/31/84	Submitted annual progress report
08/09/84	Bio/dynamics submitted four monkey protocols for toxicity study
09/19/84	Four protocols found acceptable
07/22/85	Submitted annual progress report
11/18/85	Submitted authorization for Anaquest to cross-reference IND 12,639
	Amendment to add "Production Method C" and revised Section III

DATE

EVENT

12/12/85

Transfer from Omnis to Travenol

12/16/85

Travenol authorization for Anaquest to
to cross-reference IND 12,639

Exhibit E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE : U.S. PATENT 4,250,334
ISSUED : FEBRUARY 10, 1981
TO : CLIFFORD L. COON & ROBERT L. SIMON
FOR : METHOD OF SYNTHESIZING
FLUOROMETHYLHEXAFLUOROISOPROPYL ETHER

Assistant Commissioner of Patents
Washington, D.C. 20231

S I R :

**Declaration of Mr. Kent Barta
Pursuant to 37 C.F.R. §1.740**

I, Kent Barta, declare as follows:

1. I am a patent attorney authorized to practice before the United States Patent and Trademark Office. My registration number is 29,042.

2. I have the general authority from the owner of U.S. Patent No. 4,250,334, Baxter International, Inc. (formerly, Baxter Travenol Laboratories, Inc.), to act on its behalf in patent matters.

3. I have reviewed and understand the contents of the application being submitted herewith pursuant to 37 C.F.R. §1.740.

4. After reviewing the application, I believe that U.S. Patent No. 4,250,334 is subject to extension pursuant to 37 C.F.R. §1.710.

5. I believe that an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations.

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6. I further believe that U.S. Patent No. 4,250,334, for which extension is being sought, meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

7. I further declare that all statements made herein of my own personal knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: August 7, 1995

Kent Barta
Kent Barta, Esq.

U.S. Patent No. 4,250,334
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TB48606271X

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AUG 7 '95 11:16

AUG-07-1995 15:08

708 270 2355

TOTAL P.29
212 338 9078 PAGE.029

** TOTAL PAGE.002 **
92% P.02

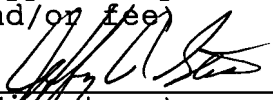


"Express Mail" mailing label number: TB 486 062 71X US
Date of Deposit: August 7, 1995

I hereby certify that the attached documents* and fees in the application for patent term extension in re U.S. Patent 4,250,334 issued Feb. 10, 1981 for METHOD OF SYNTHESIZING FLUOROMETHYL-HEXAFLUOROISOPROPYL ETHER are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date indicated above and are addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Jeffrey A. Steck

(Typed or printed name of person mailing document
and/or fee)


(Signature)

*

The original and five copies of:

- Application for Extension of Patent Term under 35 USC § 156
- Check for \$1,030.00
- Exhibit A: Copy of U.S. Patent 4,250,334
- Exhibit B: Sevoflurane Chronology of Events
- Exhibit C: Sevoflurane History
- Exhibit D: Chronology of Events of IND 12,639
- Exhibit E: Declaration of Mr. Kent Barta